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09/755,003	01/05/2001	Kevin C. Eggan	0399.2015-002	4649

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EXAMINER	
PAPPU, SITA S	
ART UNIT	**PAPER NUMBER**
1636	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/755,003	Applicant(s) EGGAN ET AL.	
	Examiner Sita Pappu	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-48 are pending in the instant application. The IDS, filed 02/07/2002 in paper # 6 and the election filed 02/07/2002 in paper #7 have been entered. This Office Action is in response to the communication filed by the Applicant in paper # 7.

Election/Restrictions

Applicants' response to the restriction, and election, with traverse, of Group II, claims 7, 13-39, 40-43, 46-48 is acknowledged. Applicants traversed the restriction requirement on the grounds that a search for the prior art for all the three Groups would not be burdensome in light of the close relationship of the Inventions. Applicants arguments have been thoroughly considered by the examiner and the restriction requirement is withdrawn and all the claims are rejoined and are being examined, herein, on their merits.

This paper contains an examination of the claims 1-48 on their merits.

Priority

Claims 42-48 do not have support in the provisional applications 60/234378 (09/20/2000) and 60/255,970 (12/15/2000) and enjoy support only in the instant application filed 01/05/2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 8, 11, 14, 18, 21, 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a transgenic mouse or transgenic mutant mouse by injecting non-inbred ES cells into tetraploid embryos, does not reasonably provide enablement for a method of producing any non-human mammal using the above method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 1, 5, 8, 11, 14, 18, 21, 41 are drawn to a method of producing non-human mammal wherein noninbred pluripotent cells are introduced into tetraploid blastocysts of the said mammal and the resulting embryo is transferred into a foster mother for the development of the offspring. The said method also includes production of mutant mammals wherein the pluripotent cells have a mutation introduced into them before

their transfer into the blastocyst. Thus, the nature of the invention is directed to transgenic animals and methods of making the transgenic animals and methods of using the transgenic animals in identifying drugs to treat a condition.

Breadth of Claims:

In the instant case, the claims 1, 5, 8, 11, 14, 18, 21, 41 are drawn to a method of producing a transgenic animal. Claims 1, 5, 8, 11, 14, 18, 21, 41 encompass the use of the said method to produce any and all non-human mammals. The specification does not provide an enabling disclosure for such a transgenic animal. The only embodiment enabled by the specification within the scope of claims 1, 5, 8, 11, 14, 18, 21, 41 is for a transgenic mouse produced by injecting non-inbred ES cells into tetraploid blastocyts of the mouse and development of the progeny. Thus the breadth of claims is very broad and the claimed method encompasses any non-human mammal and any transgenic mammal. The breadth and scope of claims 1, 5, 8, 11, 14, 18, 21, 41 thus surpass that enabled by the specification.

Amount of guidance in the specification and Working Examples:

The specification discloses the use of the said method in producing a transgenic, and/or mutant mouse. The specification and the working examples provide sufficient guidance (specification, pages 12-17) to practice the invention with only a mouse using six different F1 non-inbred lines. However, neither the specification nor the working examples provide enough guidance on how to practice the invention with any and all transgenic mammals. Although working examples are not required, particularly in the

predictable arts, the presence or absence of working examples is one factor that must be considered, particularly in the unpredictable arts.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the method with any and all transgenic mammals as claimed.

The specification fails to provide an enabling disclosure for the preparation of other species of transgenic animals besides mice because the guidance offered in the specification is limited to the preparation of mice using the method of the instant invention and no teachings or guidance are offered in regard to how one would have prepared any other type of animal. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Thus, the method of the instant invention cannot be practiced on any species other than the mouse. Since ES cell technology was required to produce the claimed animals and

practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice of the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic mice, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed in claims 1, 5, 8, 11, 14, 18, 21, 41. Thus, the enabled scope of the claims is limited to a method of producing a transgenic and/or mutant mouse by injecting non-inbred ES cells into tetraploid blastocysts and implanting them in a pseudopregnant female and development of the progeny mice from the said female mouse.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 40 is directed to a method of identifying a drug to be administered to treat a condition in a mammal by administering to a mutant mouse a drug to be assessed for its effectiveness and ability in treating or preventing the condition, wherein if the drug reduces the extent to which the condition is present or progresses, the drug is a drug to be administered to treat the condition.

The nature of invention in the case of claim 40 is directed to treating a mammal with a drug identified by using the mouse as a model organism. Claim 40 encompasses treating any and all conditions in any and all mammals by using any and all drugs and therefore has a very broad scope. The guidance provided in the specification and the working examples are insufficient in that the specification does not provide any guidance on which drugs are tested using the mouse model system and which conditions can be treated using the said drugs and in which mammal the said condition occurs and which of the candidate drugs is useful in treating or preventing a specific condition in a specific mammal. The specification does not provide sufficient guidance on how one of skill in the art can use the method of the instant invention to produce any mammal such that any drug can be tested for its effectiveness and ability to treat or prevent a condition in the said mammal. Specification discloses only a method of producing a mouse using the method of the instant invention. The specification does not disclose the phenotypes of the claimed mammals with the claimed condition or conditions such that one skilled in the art would know how to evaluate the effectiveness of the said drug in treating or preventing the said condition in any mammal. Even though the skill of an artisan in the art is high, he would be required to engage in undue experimentation, because the state of the art is such that ES cells and their use in generating adult organisms is well known only in the case of mice, and it is unpredictable how the method of the instant case can be used to produce any mammal such that the method claim 40 can practiced using the mammal produced by that method. In cases where the prior art does not enable the method, the specification must

teach the method such that one skilled in the art can accept it and practice the method without undue experimentation. Thus, the method of claim 40 is not enabled by the specification.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing XO F1 ES cells using mouse cells, comprising introducing into the Y chromosome of male F1 ES cells a negative selection marker and producing a mixture of the above male F1 ES cells and other male F1 ES cells that lack a Y chromosome, and selecting the XO F1 ES cells by subjecting the mixture to conditions that result in the death of the male F1 ES cells in which the Y chromosome has the negative selection marker inserted therein, and do not result in the death of male F1 ES cells that lack a Y chromosome and are XO F1 ES cells, does not reasonably provide enablement for a method of producing XO F1 ES cells in any mammal and or any organism . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention in the case of claim 44 is directed to a method of producing XO F1 ES cells by using negative selection to eliminate those male F1 ES cells that contain a Y chromosome such that only those male F1 ES cells that lack a Y chromosome survive and result in XO F1 ES cells. Claim 44 encompasses the use of the method of claim 44 in any organism and in any mammal and therefore has a very broad scope. The specification teaches only a method of producing XO F1 ES cells only

in mice and does not provide sufficient guidance and/or working examples to practice the method of claim 44 in any mammal and/or any organism. Further, it is known, as indicated in the rejection for claims 1, 5, 8, 11, 14, 18, 21, 41, ES cell technology is available only in mice. The specification does not provide sufficient guidance on how one of skill in the art can use the method of the instant invention to produce XO F1 ES cells in any mammal. Specification discloses only a method of producing XO F1 ES cells in a mouse using the method of the instant invention. Even though the skill of an artisan in the art is high, he would be required to engage in undue experimentation, because the state of the art is such that ES cells and their use in generating adult organisms is well known only in the case of mice, and it is unpredictable how the method of the instant case can be used to produce XO F1 ES cells in any mammal. In cases where the prior art does not enable the method, the specification must teach the method such that one skilled in the art can accept it and practice the method without undue experimentation. Thus, the method of claim 44 is not enabled by the specification in any organisms other than mice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 40, 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "mutant mouse non-inbred ES cells". There is insufficient antecedent basis for this limitation in the claim.

Claim 40 is indefinite in its recitation of "to treat a condition in a mammal in which the condition occurs, comprising producing, using the method of claim 14, a mutant mouse that is a model of the condition..."

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 40 recites the broad recitation "a mammal", and the claim also recites "a mouse" which is the narrower statement of the range/limitation.

Claim 40 is indefinite in its recitation of "the condition". Use of claim language such as "the said condition" is suggested.

Claim 40 is indefinite in its recitation of "a drug to be administered". Use of claim language such as "a candidate drug to be administered" is suggested.

Claim 41 is indefinite in its recitation of "a mutant non-human mammal, mammal". It is not clear what the Applicant is referring to. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1997, Mechanisms of Development, vol. 62, pp. 137-145) further in view of Rideout et al. (2000, Nature Genetics, vol. 24, pp 109-110).

Wang et al. (1997) teach generation of ES cell-derived mutant mice using tetraploid blastocyst injection (page 138, left column, lines 9-14; Table 2 on page 139).

Wang et al. (1997) do not teach the use of non-inbred and/or F1 ES cells in the generation of the mutant mice.

Rideout et al. (2000) teach the use of F1 ES cells (page 109, left column, paragraph 2; center column, lines 5-12) in the generation of mice and teach that genetic background has an effect on survival.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, to use F1 ES cells to inject tetraploid blasocysts and

generate mice, with a reasonable expectation of success. The motivation to do so was provided by Rideout et al. (2000) who teach that genetic background is probably an important factor in cloning efficiency and establish that F1 ES cells are efficient donor cells for generating cloned mice (page 110, center column, paragraph 2, lines 1-5) and that manipulating the F1 ES cells in vitro before cloning may allow difficult questions such as the collective role of imprinted genes in mammalian development to be addressed (see concluding paragraph, page 110).

Claims 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1997, Mechanisms of Development, vol. 62, pp. 137-145) and Uchida et al. (1995, Animal Science and technology, vol. 66, No.4, pp.361-367) further in view of Rideout et al. (2000, Nature Genetics, vol. 24, pp 109-110).

Wang et al. (1997) teach generation of ES cell-derived mutant mice using tetraploid blastocyst injection (page 138, left column, lines 9-14; Table 2 on page 139).

Wang et al. (1997) do not teach the use of non-inbred and/or generation of XO F1 ES cells and the use of those cells in the generation of the mutant mice.

Rideout et al. (2000) teach the use of F1 ES cells (page 109, left column, paragraph 2; center column, lines 5-12) in the generation of mice and teach that genetic background has an effect on survival.

Rideout et al. (2000) do not teach the generation of XO ES cells.

Uchida et al. (1995) teach the generation of XO ES cell line from an XY type ES cell line due to the loss of the Y chromosome and its use in the generation of a mouse.

Uchida et al. (1995) do not teach their method and XO ES cells in the context of tetraploid blastocyst injection or F1 ES cells. However, Uchida et al. Successfully demonstrated that an XO ES cell line can be isolated from an originally XY type cell line, and that it can be done without any negative selection (as claimed in claim 44). Uchida et al. (1995) further teach that their method and cell line is useful in producing female germ-line chimeras.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, to use the method of Uchida et al. (1995) to generate XO F1 ES cells using the male F1 ES cells as suggested by Rideout et al. (2000) to inject tetraploid blasocysts and generate mice, with a reasonable expectation of success. The motivation to do so was provided by Rideout et al. (2000) who teach that genetic background is probably an important factor in cloning efficiency and establish that F1 ES cells are efficient donor cells for generating cloned mice (page 110, center column, paragraph 2, lines 1-5) and that manipulating the F1 ES cells in vitro before cloning may allow difficult questions such as the collective role of imprinted genes in mammalian development to be addressed (see concluding paragraph, page 110) and by Wang et al. (1997) who teach that tetraploid blastocyst injection is an efficient way to minimize the and/or restrict the developmental potential of the host cells (page 137, right column, paragraph 1).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746 7442 for regular communications and (703) 746 7442 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2982.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER

S.Pappu
March 15, 2002